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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/241,347 02/02/99 BUJARD

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HM22/0708

EXAMINER

SHUKLA, R

ART UNIT

PAPER NUMBER

1632

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DATE MAILED: 07/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/241,347

Applicant(s)
Bujard And Gossen

Examiner
Ram Shukla

Group Art Unit
1632



☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-26 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

1. Claims 1-26 are pending in the instant application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-11 and 13-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse, whose genome comprises: a first transgene comprising a DNA sequence encoding a fusion protein that inhibits transcription in eukaryotic cells wherein the fusion protein comprises a tet repressor that binds to a tet operator in the absence or presence of tetracycline or tetracycline analog and that is operatively linked to a heterologous polypeptide that is selected from a group consisting of v-erb A, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5 and that inhibits transcription in eukaryotic cells and a second transgene comprising a gene of interest operatively linked to at least one tet operator sequence; and a method for modulating transcription of the second transgene in the transgenic animal by administering tetracycline or tetracycline analog to the animal, does not reasonably provide enablement for any and all transgenic non-human animals, whose genome comprises: a first transgene comprising a DNA sequence encoding any and all fusion proteins that inhibits transcription in eukaryotic cells wherein the fusion protein comprises any polypeptide that binds to a tet operator and that is operatively linked to any and all transcriptional silencer domains that inhibit transcription in eukaryotic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Claims 1-11 and 13-26 are drawn to transgenic non-human animals and methods of using such wherein a transgene (integrated in the genome of the transgenic animals) encodes a fusion protein comprising a Tet repressor and a transcription silencer domain of a protein (selected from a group of proteins) and the fusion protein binds to a tet operator sequence (operably linked to an exogenous gene) in the presence or absence of tetracycline or a tetracycline analog. Another limitation of the invention recites that the transgene is integrated to a predetermined location within a chromosome within the cells of the animals.

The specification, although enabling for the making and using of transgenic mouse that has integrated first transgene encoding a fusion protein comprising the sequence encoding the tet repressor protein (that binds to tet operator) operatively linked to the transcription silencer domain of a protein selected from a list (given earlier) and a method for modulating the expression of a gene of interest (that is also integrated in the genome of the transgenic mouse) by administering tetracyclin or tetracyclin analog, is not enabling for the making and using of any and all non-human transgenic animals that comprise a transgene that encodes a fusion protein that binds to a tet operator and that is operatively linked to the transcription silencer domain of any and all proteins because the specification does not provide sufficient guidance as to how an artisan would have practiced the invention as claimed because the art of making transgenic animals is unpredictable and has limitations, as discussed below.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Investigators observed 5-70 fold lower

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yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633,1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors.

Hammer et al (Hammer RE et al. Cell 63:1099-1112,1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. Since the claims include all animals e.g. fish, birds, insects etc., the specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address these issues?

Introduction of foreign DNA into fertilized oocytes, for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals.

Seidel (Seidel GE. J. Anim. Sci. 71(Suppl. 3):26-33, 1993) noted "In the case of livestock species.....Characterizing a transgenic line often is a greater logistical undertaking than making

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the transgenic founder. Ideally, animals should be evaluated for the transgenic trait as well as for absence of undesirable side effects in both sexes in both the hemizygous and homozygous transgenic states. Producing homozygous transgenic animals requires mating relatives, resulting in inbreeding. Characterization of transgenic lines takes many years in species with long generation intervals."

On page 18 of the specification, lines 3-17 disclose a general method of producing transgenic animal and example six discloses the method of making transgenic animal using the tetracycline operator and transactivator based regulation of the expression of an exogenous gene. However the specification does not provide any guidance as to how an artisan would have addressed the art recognized limitations of producing transgenic animals. For example, the invention as claimed encompasses all the fusion proteins that could bind to the tet operator sequence, however the specification provides disclosure about tet repressor and its mutants only. Likewise, the invention as claimed encompasses all the transcription factor domains that would have inhibited gene expression, however, the specification provides disclosures about the silencer domains of a selected list of transcription factors. Additionally, would the tet repressor/ transcriptional silencer fusion protein be active in the cells of all the species of non-human animals, particularly in view of the fact that promoter function may be dependent on the cell type due to the limitation of cellular cofactors. Furthermore, Ackland-Berglund and Leib (Ackland-Berglund CE and Leib DA. BioTechniques 18:196-200. 1995) reported that the efficacy of tetracycline-controlled gene expression is influenced by cell type.

In view of the teachings of art, as cited above, the one example of mouse in the specification is not sufficient to overcome the art recognized unpredictable nature of transgenic animal production. Given the art teachings in view of guidance provided to making transgenic mice, the artisan, at the time of filing, would have needed to engage in an undue amount of experimentation to achieve the claimed invention. As the art fails to provide guidance in the production of non-mouse transgenic non-human animal, it is encumbered upon the specification to provide those teachings that the art fails to teach. Therefore, the limitation of the scope of the claimed invention to a transgenic mouse, whose genome comprises: a first transgene comprising a DNA sequence encoding a fusion protein that inhibits transcription in eukaryotic

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cells wherein the fusion protein comprises a tet repressor that binds to a tet operator in the absence or presence of tetracycline or tetracycline analog and that is operatively linked to a heterologous polypeptide that is selected from a group consisting of v-erb A, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5 and that inhibits transcription in eukaryotic cells and a second transgene comprising a gene of interest operatively linked to at least one tet operator sequence; and a method for modulating transcription of the second transgene in the transgenic mouse by administering tetracycline or tetracycline analog to the transgenic mouse is proper.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5, 866,755 (2-2-1999).

Claims 1-26 of the instant application encompasses any and all transgenic non-human animals, whose genome comprises: a first transgene comprising a DNA sequence encoding any and all fusion proteins that inhibits transcription in eukaryotic cells wherein the fusion protein comprises any polypeptide that binds to a tet operator and that is operatively linked to any and all transcriptional silencer domains that inhibit transcription in eukaryotic cells.

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Claims 1-26 of the cited US Patent are limited in scope because they are drawn to a transgenic mouse, whose genome comprises: a first transgene comprising a DNA sequence encoding a fusion protein that inhibits transcription in eukaryotic cells wherein the fusion protein comprises a tet repressor that binds to a tet operator in the absence or presence of tetracycline or tetracycline analog and that is operatively linked to a heterologous polypeptide that is selected from a group consisting of v-erb A, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5 and that inhibits transcription in eukaryotic cells and a second transgene comprising a gene of interest operatively linked to at least one tet operator sequence; and a method for modulating transcription of the second transgene in the transgenic mouse by administering tetracycline or tetracycline analog to the transgenic mouse.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the transgenic non-human animals and the methods of controlling exogenous gene expression encompass the animals and the method taught by the US Patent No. 5,866, 755, except for a difference in the scope of the invention. The patent teaches a transgenic mouse whose genome comprises a transgene that encodes a fusion protein that comprises a tet repressor that binds to tet operator sequences and the silencer domain of a protein selected from a list of transcription factors whereas the instant application is drawn to a transgenic non-human animal whose genome comprises a transgene that encodes a fusion protein that comprises any polypeptide that binds to tet operator sequences and the silencer domain of any and all transcription factors.

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.



DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 / 630

Ram R. Shukla, Ph.D.